Transcranial Magnetic Stimulation in Therapy Studies: Examination of the Reliability of "Standard" Coil Positioning by Neuronavigation

Uwe Herwig, Frank Padberg, Jürgen Unger, Manfred Spitzer, and Carlos Schönfeldt-Lecuona

Transcranial magnetic stimulation is investigated as a new tool in the therapy of depression and other psychiatric disorders. In almost all studies, the dorsolateral prefrontal cortex (DLPFC) has been selected as the target site for stimulation. Usually this region was determined by identifying the patient's motor cortex, and from there the coil was placed 5 cm rostrally. The aim of our study was to test the reliability of this standard procedure. A neuronavigational system was used to relate the final coil position after applying the standard procedure to the individual cortical anatomy. In 7 of 22 subjects, the Brodman area 9 of the DLPFC was targeted correctly in this manner. In 15 subjects, the center of the coil was found to be located more dorsally (e.g., above the premotor cortex). The current method for locating the DLPFC is not precise anatomically and may be improved by navigating procedures taking individual anatomy into account. Biol Psychiatry 2001;50: 58–61 © *2001 Society of Biological Psychiatry*

Key Words: Transcranial magnetic stimulation, neuronavigation, therapy studies, coil positioning, dorsolateral prefrontal cortex, magnetic resonance imaging

Introduction

Several groups have investigated the therapeutic efficacy of repetitive transcranial magnetic stimulation (rTMS) above the dorsolateral prefrontal cortex (DLPFC) in depression and other psychiatric disorders (George et al 1999; Post et al 1999). The DLPFC has been selected as a target area based on neuroimaging findings such as the reduction of prefrontal glucose metabolism (Soares and Mann 1997); however, the DLPFC has not been experimentally proven to be the most effective target for therapeutic rTMS. To place the coil over the suggested position (i.e., above Brodman areas [BA] 9 and 46 as functionally relevant parts of the DLPFC), George et al (1995) and Pascual-Leone et al (1996) proposed a "standard procedure," which was then applied by nearly all investigators in this field. First, the motor cortex was localized by evoking a response of contralateral hand muscles, for instance, the abductor pollicis brevis muscle (APB). Then the coil was moved 5 cm rostrally, presumably targeting the DLPFC. The measure of 5 cm was derived from the Talairach atlas (George et al 1995; Talairach and Tournoux 1988). This method of coil placement is easy to perform but does not account for individual variations in the distance between motor areas and the DLPFC. To determine the precision of this method, we used a neuronavigational system in conjunction with magnetic resonance imaging.

Methods and Materials

We tested the standard procedure for coil placement over the DLPFC in 22 subjects (12 women, age range 21–61, 10 depressed patients and 12 healthy subjects). All subjects gave their written informed consent after the procedure had been fully explained. The protocol was approved by the local ethics committee. A neuronavigational system commonly used in neurosurgery (Surgical Tool Navigator [STN], Zeiss Oberkochen) was adapted to navigate the coil according to the individually determined anatomy (Herwig et al 1999) as visualized by high-resolution structural T1-weighted magnetic resonance imaging (MRI) (isotropic voxels $1 \times 1 \times 1$ mm, 1.5 T Magnetom Vision MR Scanner, Siemens, Germany). The STN allows the visualization of the coil location in relation to the brain in real time on a computer screen. The system is based on frameless stereotaxy, thereby avoiding head fixation. A three-dimensional camera system detects infrared light emitting diodes (LED), of which three are mounted on the subject's head using a cap and three more are fixed to the magnetic coil. A referencing procedure using anatomic landmarks is performed to coregister the head and the coil in the coordinate system of the MRI of the brain. The peak electric field under the center of the magnetic coil, calculated for a spherical head model without considering tissue conductivity and boundaries, is visualized as a line relative to the MRI on the computer screen in all three axes and in a three-dimensional reconstruction of the head surface (Figure 1). The perpendicular line through the midpoint of the figure-eight coil toward the cortex represents the maximum of the electric field that is induced by the coil.

A MagPro-Stimulator (Dantec) with a figure-eight coil (MC-

From the Department of Psychiatry, University of Ulm, Ulm, (UH, JU, MS, CS-L) and Department of Psychiatry, Ludwig-Maximilians-University of Munich, (FP), Munich, Germany.

Address reprint requests to Uwe Herwig, MD, Department of Psychiatry III, University of Ulm, Leimgrubenweg 12, D-89070 Ulm, Germany.

Received January 8, 2001; revised March 22, 2001; accepted March 27, 2001.

0006-3223/01/$20.00
PII S0006-3223(01)01153-2

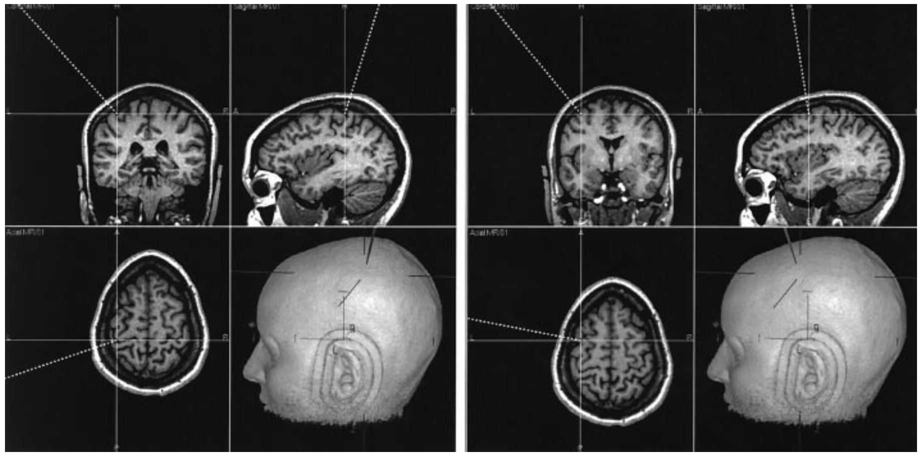

Figure 1. Visualization of the positioning on the computer screen of the neuronavigational system during stimulation. The dotted line represents the coil's peak electric field. On the left, the coil is placed above the hand knob of the left motor cortex, as indicated where the dotted line crosses the cortex. On the right, the coil is placed above the left premotor cortex after applying the standard procedure for coil positioning.

B70) and biphasic pulsewave was used to determine the individual motor threshold and the area where the most prominent motor response from the contralateral APB could be elicited during rest, holding the coil with the handle pointing from 45° dorsolaterally to laterally. The evoked motor potentials were recorded with surface electromyography (Keypoint Portable, Medtronic). Neuronavigation indicated that, in all subjects, the stimulated cortical area of APB activation was situated reliably in the region of the lateral edge of the hand knob in the left motor cortex. The coil was then placed 5 cm rostrally in a parasagittal plane, and the cortical region underneath the center of the coil was determined using the neuronavigational system (Figure 1).

The structural MRIs of the neuronavigation, with slices in all three axes, were analyzed by an experienced neuroanatomist (JU). The cortical regions in the focus of the electric field, as indicated by the dotted line, were related to the respective gyrus, to the Brodman areas, and to the Talairach coordinates (Table 1) using the Talairach atlas (Talairach and Tournoux 1988). The positions were verified by an additional transformation of the individual MRI scans into the Talairach space using the BrainVoyager software (BrainInnovation) in 17 of the 22 subjects. The derived Talairach coordinates of all subjects were visualized together on an individual Talairach transformed surface rendered MRI (Figure 2).

To determine whether head size influences localization, we measured the individual distance from the nasion to the most distant occipital point of the skull, generally the inion, in the midsagittal plane. We then compared the measures between the groups with a positioning above BA 6 (4 women, 3 men) and above BA 9 (5 women, 2 men) using a one-way ANOVA.

Results

In all subjects, the standard procedure resulted in placement of the midpoint of the coil above the area of the middle frontal gyrus (MFG); however, the precise position varied considerably between subjects, ranging from the premotor cortex (PMC) to the DLPFC (Table 1). In 7 of the 22 subjects, the coil was placed over the PMC (BA 6). In five subjects, the coil was placed above the borders of the PMC and the DLPFC, above the borders of BA 6 to BA 8 respectively. In three subjects, the coil was located above BA 8 in the MFG, a part of the DLPFC that is generally defined as frontal eye field (FEF). Seven measurements (32%) were located above BA 9 (one of them on the border to BA 8), as originally intended by the standard procedure.

Within the MFG, the coil positions ranged in the superior–inferior direction from the border between the superior frontal gyrus (SFG) and the MFG to the inferior part (IP) of the MFG. In the majority of the subjects, the coil was placed above the superior part (SP) of the MFG.

The mean anterior–posterior distance between the *y* values of the Talairach coordinates was 40 mm, not 50 mm as the principle of the coil positioning would imply. This may be because the distance above the cortex is on a smaller radius than the distance above the scalp. The ranges of the *x*/*y*/*z* Talairach coordinates in the anterior position were 22/18/17 mm, whereas the ranges for the motor cortex were 6/10/6 mm, reflecting the resulting interindividual differences of the standard positioning. The initial positioning, obtained by determining the motor threshold, was in the region of the hand knob of the motor cortex in all subjects (Figure 2). Analysis of the effect of head size on coil location revealed no significance.

Discussion

In our study, we investigated the accuracy of the standard procedure for coil positioning, which is commonly applied in treatment trials with rTMS above the DLPFC. We found a reliable positioning of the coil above the MFG; however, in 15 of 22 (68%) of our subjects, the coil was not placed

Table 1. Talairach coordinates of coil positions of APB response and after application of the standard positioning for transcranial magnetic stimulation ($N = 22$)

Subject No.	Talairach coordinates APB response	Talairach coordinates after standard positioning APB + 5 cm	Anatomic region APB + 5 cm	Brodman area APB + 5 cm	Head length [mm]
1	38/−26/58	38/10/52	pmc mfg sp	6	197
2	36/−24/60	35/12/53	pmc mfg sp	6	203
3	35/−28/60	40/08/53	pmc mfg sp	6	206
4	36/−28/60	41/10/47	pmc mfg sp	6	196
5	38/−26/58	30/16/55	pmc mfg sp	6	185
6	40/−28/56	35/10/52	pmc mfg/sfg	6	200
7	36/−28/60	36/10/55	pmc mfg/sfg	6	199
8	38/−20/58	32/18/52	dlpfc/pmc mfg sp	6/8	201
9		30/22/52	pmc/dlpfc mfg sp	6/8	192
10	40/−26/58	42/12/47	dlpfc/pmc mfg sp	6/8	204
11	38/−24/58	38/15/48	dlpfc/pmc mfg sp	6/8	205
12		36/14/46	dlpfc/pmc mfg sp	6/8	208
13	35/−18/60	26/26/53	dlpfc mfg/sfg	8	182
14	36/−24/60	40/20/45	dlpfc mfg sp	8	196
15	40/−22/56	35/22/50	dlpfc mfg sp	8	203
16	36/−20/60	42/18/42	dlpfc mfg sp/ip	8/9	188
17	38/−18/60	48/26/38	dlpfc mfg sp/ip	9	189
18	34/−22/62	44/18/38	dlpfc mfg sp/ip	9	187
19	38/−24/58	46/18/40	dlpfc mfg sp/ip	9	203
20	40/−18/60	48/22/38	dlpfc mfg sp/ip	9	182
21	38/−20/62	43/22/40	dlpfc mfg sp/ip	9	211
22		47/18/38	dlpfc mfg ip	9	192
Mean	37/−23/59	39/17/47			197
Range	6/10/6	22/18/17			29
±SD	2/4/2	6/5/6			9

Coordinates indicate the optimal site for eliciting a motor response in the abductor pollicis brevis muscle (APB-response for 19 subjects; for three subjects, only the images of the rostral positioning were saved), and 2) the region after placing the coil 5 cm rostrally (APB + 5 cm). For the latter, anatomic regions and the respective Brodman areas (BA) are also given, as well as the head length of each subject.

APB, abductor pollicis brevis muscle; DLPFC, dorsolateral prefrontal cortex; IP, inferior part; MFG, middle frontal gyrus; PMC, premotor cortex; SFG, superior frontal gyrus; SP, superior part.

above BA 9 in the DLPFC as intended. Instead, it was located above BA 6 or BA 8, the PMC or the FEF, respectively. Thus, the stimulation sites were located more posteriorly and superiorly relative to BA 9. Therefore, the 5-cm measure taken from the Talairach brain appears to be to short in order to target BA 9. Individual head size in our sample was not identified as a factor for the anterior–posterior variations of coil placement.

With respect to the treatment of depression, our results put in perspective reports of modest antidepressant effects of rTMS (George et al 1999; Padberg et al 1999). Because most studies that investigated therapeutic efficacy used the standard procedure for coil placement, it is likely that rTMS was performed at cortical sites that were not necessarily involved in the pathophysiologic mechanisms of depression. In other words, lacking or minor therapeutic effects reported in previous studies could be explained by not having stimulated the intended area of the DLPFC.

Based on our results, we propose the use of neuroimaging—and if possible neuronavigational methods—for coil placement to account for individual neuroanatomy. If neuronavigation is not available, it may be possible to position the coil based on an individual MRI scan, identifying the lateral edge of the hand knob and measuring the individual distance and direction to the DLPFC; however, this procedure needs further validation by neuronavigational methods.

Independent of the detection of the precise anatomic region, as investigated by this methodologic study, we suggest that the DLPFC has not yet been confirmed as the optimal target area for antidepressant rTMS. For example, there are no studies comparing the stimulation of the DLPFC with the stimulation of other prefrontal areas. More empirical data are required to target precisely therapeutic rTMS. Furthermore, functional neuroimaging studies of higher cognitive functions, specifically those impaired in major depression, may be informative for more effective TMS targeting in depression.

Conclusion

The standard procedure for targeting TMS to the DLPFC in treatment studies does not provide reliable positioning. While it is still subject to proof if the areas BA 9 and 46

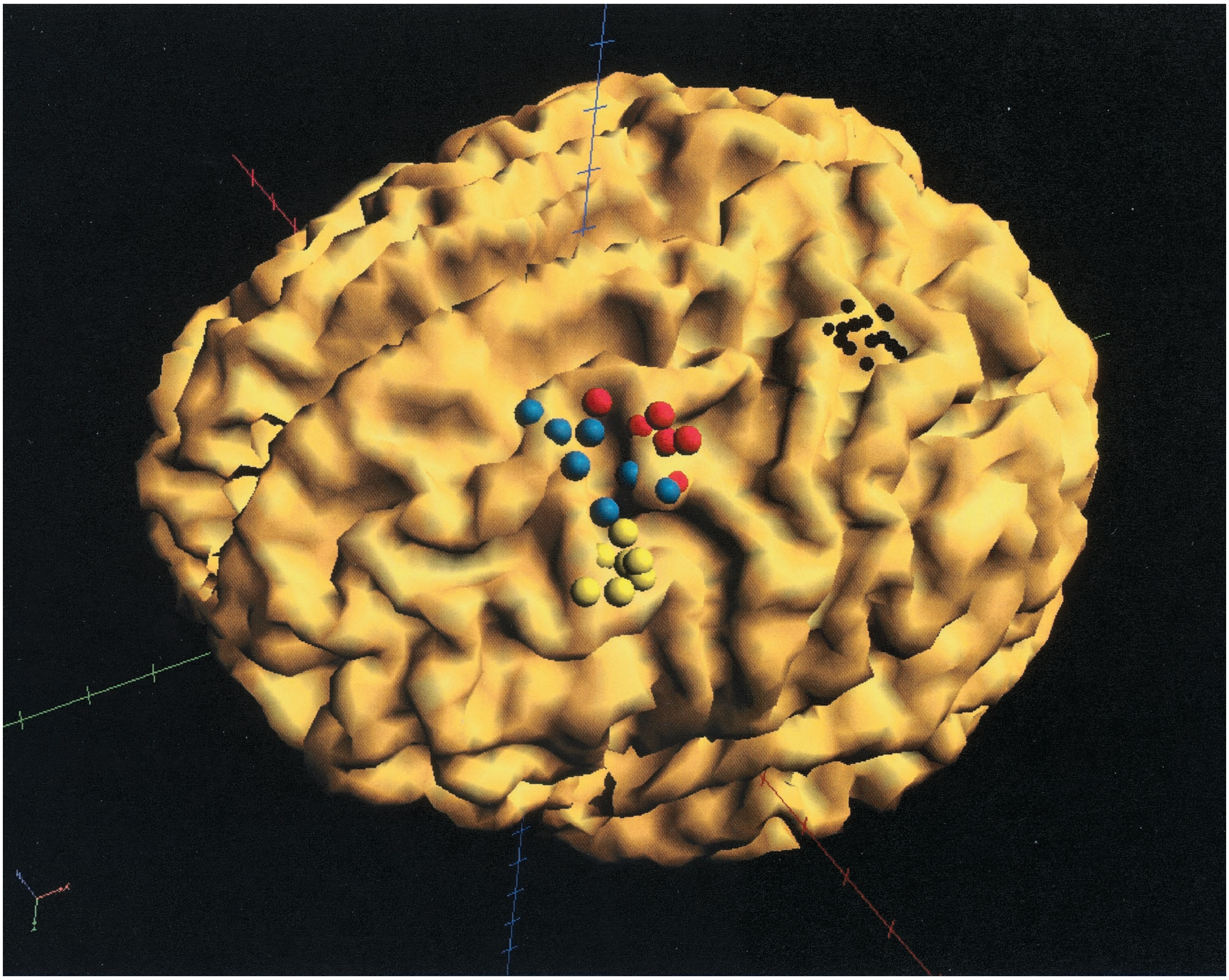

Figure 2. The individual Talairach coordinates before and after standard positioning of the coil are visualized in an individual surface rendered magnetic resonance image of the brain (white matter segmentation) that was transformed into Talairach space (view onto the left frontal cortex). The small black dots indicate the optimal sites for abductor pollicis brevis muscle stimulation over the motor cortex (i.e., the region around the lateral edge of the hand knob). The larger dots indicate the rostral coil positions over the different Brodman areas: red BA 6, blue BA 6/8 and 8, yellow BA 8/9 and 9.

of the DLPFC are the relevant target areas for therapeutic rTMS, neuronavigation based on individual anatomy can improve precision of coil positioning and may lead to a superior therapeutic effect of prefrontal rTMS.

References

George MS, Lisanby SH, Sackeim HA (1999): Transcranial magnetic stimulation: Applications in neuropsychiatry [comment]. *Arch Gen Psychiatry* 56:300–311.

George MS, Wassermann EM, Williams WA, et al (1995): Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. *Neuroreport* 6:1853–1856.

Herwig U, Schönfeldt Lecuona C (1999): Neuronavigation in psychiatry—focused transcranial magnetic stimulation in depressed patients [in German]. *Nervenheilkunde* 18:353–357.

Padberg F, Zwanzger P, Thoma H, Kathmann N, Haag C, Greenberg BD, et al (1999): Repetitive transcranial magnetic stimulation (rTMS) in pharmacotherapy-refractory major depression: Comparative study of fast, slow and sham rTMS. *Psychiatry Res* 88:163–171.

Pascual-Leone A, Rubio B, Pallardo F, Catala MD (1996): Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression [see comments]. *Lancet* 348:233–237.

Post RM, Kimbrell TA, McCann UD, et al (1999): Repetitive transcranial magnetic stimulation as a neuropsychiatric tool: Present status and future potential. *J ECT* 15:39–59.

Soares JC, Mann JJ (1997): The functional neuroanatomy of mood disorders. *J Psychiatr Res* 31:393–432.

Talairach J, Tournoux P (1988): Co-Planar Stereotaxic Atlas of the Human Brain. New York: Thieme Medical Publishers.